Hepatocellular Carcinoma : Treated with Hepatic Arterial Embolization, an Analysis of Prognostic Features in 150 Cases

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Abstract

From July 1989 to July 1999, 120 male and 30 female patients with hepatocellular carcinoma (HCC), whose ages ranged from 18 to 71 years, were treated by different modalities. The patients were divided into 3 groups according to treatment modalities : group 1 consisted of 35 cases treated by transarterial embolization (TAE) using gelatin sponge permeated with mitomycin-c 20 mg, group 2 - 100 cases treated by transcatheter oily chemoembolization (TOCE) using lipiodol 10 cc with mitomycin-c 20 mg together with gelatin sponge for hepatic embolization, and group 3 - 15 cases treated by TOCE followed by surgical wedge hepatic resection.

The prognostic features following treatments were retrospectively analysed in relation to therapeutic modalities. The results revealed that TOCE was superior to TAE and that TOCE plus adjunct wedge hepatic resection was the best treatment modality with the best cumulative surgical rate (median survival 46.69 months).

Analysis of the life-table methods of group 2 patients revealed that the stage of tumors and serum biochemistry on entry, both of which corresponded well with hepatic reserve function were statistically significant prognostic factors for treatment result and long-term outcomes. Further analysis of all the patients also revealed that tumor size and stage of tumors were significant prognostic factors for the treatment of hepatocellular carcinomas.

Key word : Hepatocellular Carcinoma, Embolization, Hepatic Resection

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Hepatocellular carcinoma is a common neoplasm world-wide with poor prognosis[1-4] and is particularly common in Asia[5-7]. Currently, surgical resection of hepatocellular carcinoma is the only radical treatment which may prolong survival of the patients[8-10]. Unfortunately, the resectable rate of hepatocellular carcinoma is very low because of gigantic tumor size, extent of disease at the time of diagnosis, location of the tumor, histologic type of the tumor and the high incidence of concurrent hepatic parenchymal disease. Thus, only 10 per cent of hepatocellular carcinoma are amenable to operative resection[11-14]. Various types of treatment for unresectable tumor have been attempted such as chemotherapy[15-17] and hepatic artery ligation[18] without any satisfactory result. Since 1976, hepatic arterial embolization has shown a remarkable antitumor effect and it is accepted as the first choice of therapy for unresectable hepatocellular carcinoma [19]. In 1989, Nakamura et al[20] introduced transcatheter oily chemoembolization (TOCE) and this technique is now universally accepted as the method of choice for the treatment of inoperable hepatocellular carcinoma[21].

Recent concepts of converting unresectable to resectable hepatocellular carcinoma have been proposed such as preoperative radiation of the tumor or preoperative transcatheter embolization of the tumor in order to decrease tumor bulk, tumor size, tumor neovasculatures, and have resulted in prolonged survival of the patients[22,23].

The main purposes of this article were :

1. To analyse and compare the treatment results of different treatment modalities, among transarterial embolization (TAE), transcatheter oily chemoembolization (TOCE) and combined TOCE and surgical wedge hepatic resection.

2. To analyse other important prognostic factors on treatment results and patient survival.

MATERIAL AND METHOD

From July 1989 to July 1999, 150 consecutive patients were diagnosed at Ramathibodi Hospital in Bangkok with hepatocellular carcinoma (HCC) based on histological examination by liver biopsy in all cases. The 120 males and 30 females ranged in age from 18 to 71 years. Ninety patients (60%) were cirrhotic patients which belonged to Child's grade A or B patients according to Child's criteria[24]. Ninety patients (60%) had high levels of serum alfa fetoprotein (AFP) measured by radioimmunoassay prior to treatment. One hundred and two patients (68%) had positive serum hepatitis B surface antigen measured by a commercially available radioimmunoassay kit. Other biochemistry values such as serum SGOT, SGPT, albumin, and bilirubin were obtained in all cases prior to treatment. All patients were classified as stage 2 or stage 3 according to Okuda's classification[25]. Periodic surveillance was carried out with serum AFP determination and imaging using CT scan (group 1) and lipiodol CT scan (group 2 and 3) at 4 week intervals.

A repeated TAE or TOCE was performed after 6 weeks when CT scan or lipiodol CT scan showed residual tumor[26].

Prior to embolization, hepatic arteriography was performed to obtain information about the size, type, location, and feeding artery of the tumor. The portal vein was seen in all cases by obtaining venographic phase of superior mesenteric or splenic arteriogram.

All the patiients were divided into 3 groups according to the different treatment modalities as :

Group 1 : comprised 35 patients who underwent percutaneous transarterial chemoembolization (TAE) with the catheter being inserted superselectively into the hepatic artery that fed the tumor. A gelatin sponge block (gelfoam : Upjohn, Kalamazoo, MI, USA) was cut into 1- to 2-mm pieces and permeated with antineoplastic agent (20 mg of mitomycin-c) and a contrast material (60% urografin [meglumine and sodium diatrizoate]). Under fluoroscopic guidance, these embolic materials were infused into the feeding arteries until cession of blood flow. (Fig. 1-2).

Group 2 : comprised 100 patients who underwent treatment with transcatheter oily chemoembolization (TOCE) using a mixture of an iodized oil (lipiodol : André Guerbet. Aulnay-sous-zois, France) 10 ml with an anticancer drug (mitomycin-c) 20 mg infused into the tumor feeder artery or arteries selectively and the feeder artery was finally embolized with gelatin sponge 1-2 mm, cut into pieces under fluoroscopic guidance until cessation of blood flow. The lipiodol could be seen in plain film of the abdomen or by lipiodol CT scan obtained 4 weeks after TOCE (Fig. 3-4).

Group 3 : comprised 15 patients who underwent treatment with TOCE or repeated TOCE

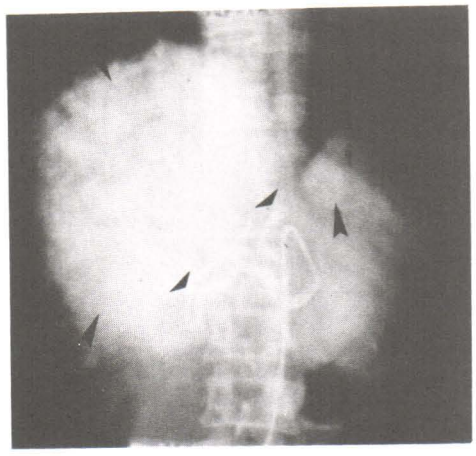

Fig. 1. Delayed arterial phase, celiac angiogram post TAE of a patient with HCC shows multiple masses of HCC in both liver lobes (big arrow). Peripheral branches of the hepatic arteries are occluded by TAE (small arrow).

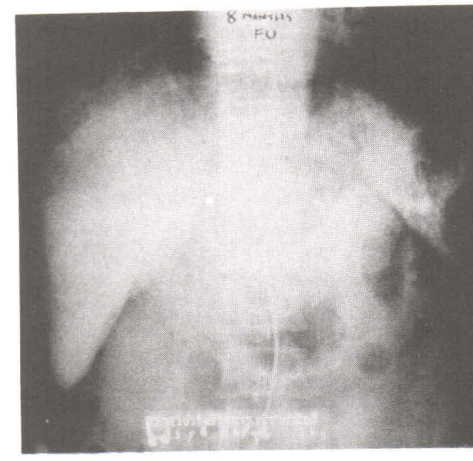

Fig. 2. Hepatogram (same case as Fig. 1) 8 months after 2 sessions of TAE shows much improvement of HCC with almost normal appearance of liver.

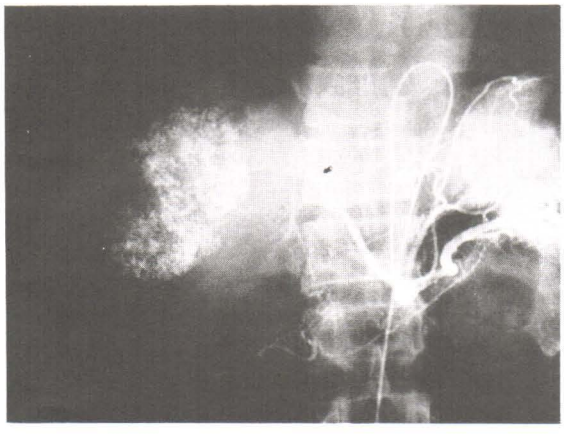

Fig. 3. Celiac angiogram, arterial phase shows complete embolization of tumor feeder by gelfoam particles (small arrow) lipiodol stain (big arrow) seen from transcatheter oily chemoembolization (TOCE).

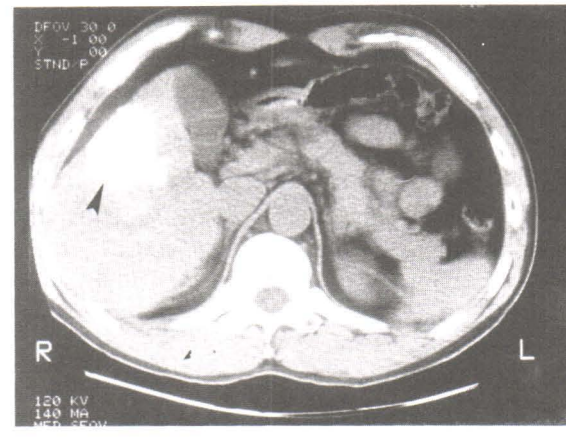

Fig. 4. Same case as in Figure 3, lipiodol CT scan following repeated TOCE shows a complete opacification of HCC by lipiodol (arrow) representing necrosis of the tumor.

(as described in group 2) until the tumor was feasible for surgical resection illustrated by followed up lipiodol CT scan, also by low or normal level of serum AFP with the tumor size close to or equal to 5 centimeters measured by followed-up enhanced CT scan of the upper abdomen. The tumor was resected surgically by using ultrasonic resector with wedge hepatic resection. The wedge hepatic resection was performed in all surgical cases 2 to 4 weeks after the last TOCE. The patients were followed periodically after surgery as described.

Statistical Analysis

A one-sample Kolmogorov-Smirnov test was used to investigate whether the concentrations of SGOT, SGPT, Albumin were normally distri-

Table 1. Clinical features of patients with hepatocellular carcinoma at entry.

	Group 1 (TAE)	Group 2 (TOCE)	Group 3 (TOCE + HEPATECTOMY)
Number of cases	35	100	15
Sex (Male : Female)	31 : 4	77 : 23	12 : 3
Cirrhosis (Positive : Negative)	21 : 14	57 : 43	12 : 3
HBs Ag (Positive : Negative)	19 : 16	71 : 29	11 : 4
STAGE (II : III)	9 : 26	47 : 53*	13 : 2*†
Tumor Size (cm.)	14.69 ± 4.58	10.23 ± 3.49	6.633 ± 1.37*†

* Statistically significant different from group 1

† Statistically significent different from group 2

buted. To compare the two stages within group 2 (TOCE), unpaired t-test and Mann-Whitney tested in total bilirubin were used. Tumor size differences between groups were tested by Kruskall-Wallis test and multiple comparison test (Student-Neuman-Keuls). Proportion difference between groups was done by chi-square test. Cumulative survival was determined by using the Kaplan-Meier method from the time of treatment modalities and the differences between survival rates were tested with the Log Rank method. A p-value < 0.05 was considered statistically significant.

RESULTS

Details of the clinical features of patients with hepatocellular carcinoma on admission are shown in Table 1. Group 1 consisted of 35 patients; group 2 consisted of 100 patients, and group 3 consisted of 15 patients. The statistical analysis in Table 1, shows that only tumor size and staging of tumors had a statistically significant difference among the 3 groups (p-value < 0.05). There was no statistical difference in sex, positive cirrhosis, positive HbsAg among the 3 groups.

In regard to the staging and biochemistry of patients, we used sampling from group 2 as our study cases since it had the greatest number of patients (100 cases) among the 3 groups. Statistical study showed that there was a significant difference in the distribution of serum biochemistry including serum SGOT, SGPT, Albumin and bilirubin between stage 2 and stage 3 in group 2 patients. The stage 2 patients had better serum biochemistry or better liver reserve function than stage 3 patients (Table 2).

The cumulative survival of group 1, group 2 and group 3 is illustrated in Fig. 5. The median survival of group 1 (TAE), group 2 (TOCE) and group 3 (TOCE + hepatic resection) was 8.38 months, 16.27 months and 46.69 months respectively.

The actual survival rates for the 1 and 2 year periods were 32.1 per cent and 12 per cent respectively for group 1, 54.7 per cent and 25.9 per cent respectively for group 2, 93.3 per cent and

Table 2. Comparing the serum biochemistry (Mean ± SEM) of stage 2 and stage 3 in group 2 patients with hepatocellular carcinoma at entry.

Biochemistry	Stage 2 (n=32)	Stage 3 (n=34)	Significance p
SGPT (U/L)	68.53 ± 9.60	106.38 ± 14.22	0.033
SPOT (U/L)	107.53 ± 15.71	186.14 ± 21.01	0.004
Total Bilirubin (Umol/L)	29.38 ± 6.07	43.00 ± 8.59	0.0389
Albumin (g/L)	36.93 ± 1.32	32.02 ± 1.59	0.022

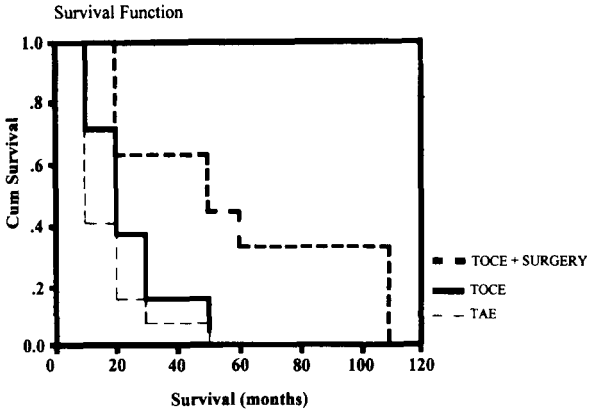

Fig. 5. **Cumulative survival of patients with hepatocellular carcinoma with different treatment modalities. There is a significantly better cumulative survival rate after transcatheter oily chemoembolization (TOCE) plus surgical resection (median survival of 46.69 months) compared to transarterial oily chemoembolization (TOCE) alone (median survival of 16.27 months) and much better than transarterial embolization (TAE) alone (median survival of 8.38 months).**

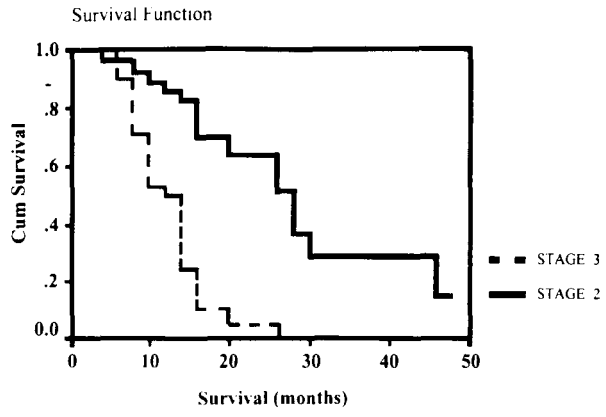

Fig. 6. **Cumulative survival of patients with hepatocellulae carcinoma treated with transcatheter oily chemoembolization (TOCE) alone (group 2). There is a significantly better prognostic factor in stage 2 patients (median survival 26 months) than stage 3 patients (median survival 11.97 months).**

60.3 per cent respectively for group 3 patients (Table 3).

Fig. 6 illustrates the cumulative survival rate of stage 2 and stage 3 in group 2 patients. The median survival was 26 months and 11 months respectively.

Complications

Pain, nausea, vomiting and low-grade fever were related to TAE or TOCE. The symptoms were transient and recovery was achieved by symptomatic treatment. However, recovery of hepatic function was delayed for 10 or 14 days. Biochemistry values in some cases became elevated to more than two or three times the pre-embolized levels and gradually decreased in level in 14 days. Patients with TAE had more elevation of serum biochemistry than the other groups. Severe hepatic failure and encephalopathy were found in most end-stage cases; and these patients eventually died from hepatic failure. Liver abscess was found in 2 cases (1.3%) from contamination of gelfoam during TAE.

Table 3. Survival rate of patients with hepatocellular carcinoma in different treatment modalities.

Group	Survival					
	6 months %	1 year %	2 years %	3 years %	4 years %	5 years %
TAE	42.8	32.1	12.0	-	-	-
TOCE	82.5	54.7	25.9	14.8	7.4	-
TOCE + Surgery	93.3	93.3	60.3	43.1	43.1	32.3

TAE = Trans - arterial embolization
TOCE = Trans -catheter oily chemoembolization

Four patients had uric acid nephropathy (2.66%) and eventually died from renal failure. Two patients (1.3%) developed acute onset of cholecystitis caused by reflux of gelfoam into the cystic artery and cholecystectomy had to be performed in both cases.

Ruptured esophagus varices was seen in 3 cases (2%). Active GI bleeding from duodinitis, gastitis, duodenal ulcer or peptic ulcer was seen in 2 cases (1.3%).

Table 4. Comparison of survival rates of patients with HCC treated by TAE & TOCE at Ramathibodi Hospital with those in Nakamura's article[20].

	Ramathibodi Hospital		Nakamura[20]	
	TAE	TOCE	TAE	TOCE
6 Months	42.8 %	82.5 %	67.4 %	82.0 %
1 years	32.1 %	54.7 %	45.2 %	53.8 %
2 years	12 %	25.9 %	16.3 %	33.3 %

TAE = Transarterial embolization
TOCE = Transcatheter oily chemoembolization

Four cases (2.66%) developed pancytopenia, after repeated TAE and TOCE. The occurrence was observed from 9 to 24 months following the first TAE or TOCE. Metastasis was seen 4 months to 48 months from the first TAE or TOCE or after TOCE plus wedge hepatic resection. Lung metastasis was the most common (12 cases, 8.7%). Bone metastasis was found in 2 cases (1.3%) and one patient died from brain metastasis (0.66%).

DISCUSSION

From our data which was compatible with that of Nakamura et al[20] (Table 4), demonstrated that treating HCC with TOCE had a better survival rate than TAE. Nakamura noted that TAE using gelfoam soaked with an anticancer drug had a remarkable effect on an encapsulated tumor not larger than 4 centimeters fed by arterial blood which was also noted by other authors[27-29]. However, TAE is not effective in treating extracapsular infiltrative lesions or daughter nodules in the liver fed by sinusoidal blood or the portal vein, which communicates with the sinusoid[30]. This can be explained by the fact that gelfoam particles which are used in TAE can migrate only as far as arteriole, but can not reach the sinusoid. With additional lipiodol used in TOCE, lipiodol acting as a carrier of antitumor drug can migrate as far as the sinusoid supplying blood to daughter nodules. Lipiodol-in-water emulsion will finally release the antitumor drug to the daughter nodules and hence explains the effectiveness of TOCE on this tumor. This daughter nodule or extracapsulated infiltrative tumor is seldom detected by CT scan after TAE but can be detected by lipiodol CT scan after TOCE.

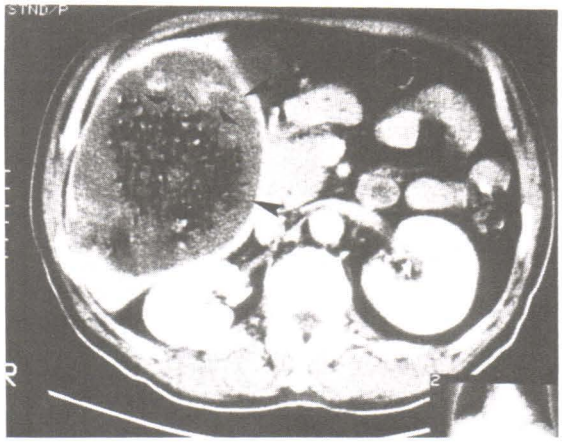

Fig. 7. Water soluble contrast enhanced CT scan 2 weeks after TAE shows low attenuation and nonenhanced area of tumor (big arrow) representing tumor necrosis (CT number ≤ 30 HU). Note some air streak in the tumor probably from introduction during TAE (small arrow).

The direct antitumor effect from TAE or TOCE is coagulation necrosis of the tumor tissue which can be demonstrated in TAE with a marked decrease in serum AFP levels, selective disappearance of tumor vessels and isolated decrease in tumor density in the angiogram corresponding well with decreased density in the CT scan (Fig. 7). In TOCE, it results in complete opacified necrotic tumor (Fig. 4). However, after a good result with TAE or TOCE by normalization of serum AFP, viable tumor cells could still be identified beneath the capsule seen in our surgical cases which is similar to another study[31]. Therefore, final wedge hepatic resection should be performed in order to achieve complete removal of the tumor and result in a long term effect of treatment. The statistical analysis confirmed that the best cumulative survival rate was achieved by a combination of TOCE and adjunct wedge hepatic resection. In Table 5, data of the median survival from Ramathibodi Hospital (our data) and that of Hiroshi et al[32] are compared, and compatiblility was found. There is evidence of improvement in median survival if additional hepatic resection is undertaken in patients with TOCE. Since it has been suggested that manipulation of the tumor during surgery may facilitate the spread of HCC cells[33], we repeated TOCE pre-

Table 5. Comparison of median survival (in months) of patients with HCC treated by TOCE plus hepatic resection at Ramathibodi Hospital with that in Hiroshi's article[32].

Ramathibodi Hospital		Hiroshi[32]	
TOCE	TOCE + Hepatic resection	TOCE	TOCE + Hepatic resection
12.67 Months	46.69 Months	32 Months	67.5 Months

TOCE = Transcatheter oily chemoembolization

operatively. We decided to do wedge hepatic resection as early as 2 to 4 weeks after the last TOCE, which was different from other series[22,31]. The reason was to prevent metastatic seeding which may occur because of a longer period between TOCE and surgery. Although adjunct wedge hepatic resection is one of the most important and highly prognostic factors after hepatic embolization, the hepatic reserve function judged by serum biochemistry such as serum albumin, bilirubin, SGOT, SGPT levels are also significant prognostic factors in patients with HCC (Table 2). From the statistical analysis, the staging of patients may correlate well with hepatic reserve function or serum biochemistry (Table 2). The cumulative survival rates for stage 2 patients were significantly better than stage 3 (Fig. 6). From Table 1, patients with small tumors were found to have a significantly better prognosis. Patients in group 3, who had resectable tumors, all had small tumors. Although some patients in this group had gigantic tumors, the tumor could be reduced to surgical resectable size after repeated TOCE. Patients in this group also had good hepatic reserve function on admission.

In conclusion, the best treatment for HCC is TOCE plus wedge hepatic resection. TOCE has better results than TAE. The prognostic factors that will determine the treatment are the tumor size, the staging of the tumor and the biochemistry or reserve function of the liver.

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การรักษามะเร็งตับชนิดปฐมภูมิโดยการอุดกั้นหลอดเลือดผ่านหลอดสวน การวิเคราะห์ปัจจัยต่าง ๆ ในการรักษาผู้ป่วย

ชรินทร์ เอื้อวิไลจิต, พ.บ., เอาชัย กาญจนพิทักษ์, พ.บ.***

ตั้งแต่เดือนกรกฎาคม ปี พ.ศ. 2532 จนถึงกรกฎาคม ปี พ.ศ. 2542 ได้ทำการรักษามะเร็งตับชนิดปฐมภูมิจำนวน 150 ราย อายุ 18 ปี ถึง 71 ปี ผู้ป่วยเป็นผู้ชาย 120 ราย ผู้หญิง 30 ราย ซึ่งแบ่งผู้ป่วยทั้งหมดนี้ออกเป็น 3 กลุ่ม ตามวิธีการรักษา กล่าวคือ ผู้ป่วยกลุ่มที่ 1 มี 35 ราย รับการรักษาด้วยการอุดกั้นหลอดเลือดผ่านหลอดสวน โดยใช้สารอุดกั้นหลอดเลือดที่เรียก เจลโฟม ชุบยาไมโตรไมซิน ซี ซึ่งเป็นยายับยั้งการเจริญของมะเร็งตับชนิดหนึ่ง ขนาดยา 20 มิลลิกรัม ฉีดเข้าหลอดเลือดตับที่เลี้ยงมะเร็ง กลุ่มที่ 2 มีผู้ป่วยจำนวน 100 ราย รับการรักษาด้วยการฉีดสารไมโตรไมซิน ซี 20 มิลลิกรัม เขย่ากับสารลิพิโอโดซึ่งเป็นสารทึบรังสีทำจากน้ำมันพืชฝิ่น 10 ซีซี ผ่านหลอดสวนเข้าไปในหลอดเลือดของตับที่ไปยังก้อนมะเร็ง แล้วอุดกั้นหลอดเลือดนี้อีกทีด้วยสารเจลโฟม ส่วนกลุ่มที่ 3 มีผู้ป่วย 15 ราย รับการรักษาตามที่กล่าวมาในกลุ่มที่ 2 แต่จะผ่าตัดเอาก้อนมะเร็งออกหลังรักษาตามกลุ่มที่ 2 สักระยะหนึ่งจนสามารถผ่าตัดก้อนมะเร็งออกได้

จากการวิเคราะห์โดยวิธีทางสถิติต่าง ๆ พบว่า ผู้ป่วยกลุ่มที่ 3 มีอัตราการอยู่รอดของผู้ป่วยสูงที่สุด ผู้ป่วยกลุ่มที่ 2 มีอัตราการอยู่รอดสูงกว่ากลุ่มที่ 1 ซึ่งแสดงว่า การรักษาแบบวิธีที่ใช้ในกลุ่ม 3 เป็นการรักษาผู้ป่วยมะเร็งตับชนิดปฐมภูมิที่ดีที่สุด นอกจากนี้จากการวิเคราะห์ทางสถิติยังพบว่า ผลการรักษาที่ทำให้อัตราการอยู่รอดสูง ยังขึ้นกับขนาดของก้อนมะเร็ง ถ้ามีขนาดเล็กจากการทำการรักษาดังกลุ่มที่ 3 จนก้อนมะเร็งมีขนาดเท่ากับหรือต่ำกว่า 5 เซนติเมตร แล้วทำการผ่าตัดก้อนมะเร็ง จะได้อัตราการอยู่รอดของผู้ป่วยสูงสุด นอกจากนี้อัตราการอยู่รอดของผู้ป่วยนี้ยังขึ้นกับผลเลือดซึ่งส่อถึงการทำงานของตับ ถ้าผลเลือดนี้มีค่าใกล้เคียงกับค่าปกติ แสดงว่าการทำงานของตับของผู้ป่วยในรายนั้น ๆ อยู่ในขั้นดี จะได้อัตราการอยู่รอดของผู้ป่วยในรายนั้น ๆ อยู่ในขั้นดี จะได้อัตราการอยู่รอดของผู้ป่วยหลังการรักษาสูงด้วย

คำสำคัญ : มะเร็งตับปฐมภูมิ, การอุดกั้นหลอดเลือด, การผ่าตัด

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